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2. SUMMARY OF SAFETY AND EFFECTIVENESS

This summary of 510(k) safety and effectiveness information is being submitted in accordance with the requirements of SMDA 1990 and 21 CFR 807.92.

The assigned 510(k) number is: K032554

GEN-PROBE® APTIMA® Combo 2 Assay
GEN-PROBE® APTIMA® Vaginal Swab Specimen Collection Kit

Sponsor/Contact Information

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General Information

Trade Name: GEN-PROBE® APTIMA® Combo 2 Assay

Common or Usual Name: Ribosomal RNA (rRNA) target-amplified nucleic acid probe test for the *in vitro* diagnostic detection of *Chlamydia trachomatis* and/or *Neisseria gonorrhoeae*

Classification Names: DNA Probe, Nucleic Acid Amplification, Chlamydia
DNA Reagents, Neisseria

APTIMA Combo 2 Assay

Device Description	DNA Probe, Nucleic Acid Amplification, Chlamydia
Medical Specialty	Microbiology
Product Code	MKZ
Device Class	1
Regulation number	866.3120

Device Description	DNA Reagents, Neisseria
Medical Specialty	Microbiology
Product Code	LSL
Device Class	2
Regulation number	866.3390

Substantially Equivalent Devices:
APTIMA Combo 2 Assay; K003395

Device Description

Clearance of this premarket notification extends the clinical performance claims of the commercially available GEN-PROBE APTIMA Combo 2 Assay to include clinician-collected and patient-collected vaginal swabs (in a medical setting) as acceptable testing specimens. The ancillary kit formulated for this specific application is the GEN-PROBE APTIMA Vaginal Swab Specimen Collection Kit. The components of the APTIMA Vaginal Swab Specimen Collection Kit include: (1) a sterile swab for the collection of vaginal specimens and (2) a transport tube containing transport media with a penetrable cap.

The APTIMA Vaginal Swab Specimen Collection Kit is for use with the APTIMA Assays for the detection of *Chlamydia trachomatis* and *Neisseria gonorrhoeae*. The APTIMA Vaginal Swab Specimen Collection Kit is intended to be used for clinician and patient collection of vaginal swab specimens according to the instructions provided. The APTIMA Vaginal Swab Specimen Collection Kit not for home use.

The background information describing the relevant diseases, *Chlamydia trachomatis* and *Neisseria gonorrhoeae*, and the principles of the APTIMA Combo 2 Assay are provided in the Summary of Safety and Effectiveness for the APTIMA Combo 2 Assay (K003395)

Intended Use

AC2 Assay package insert:

The APTIMA Combo 2 Assay is a target amplification nucleic acid probe test that utilizes target capture for the *in vitro* qualitative detection and differentiation of ribosomal ribonucleic acid (rRNA) from *Chlamydia trachomatis* and/or *Neisseria gonorrhoeae* in clinician-collected endocervical, vaginal, and male urethral swab specimens, patient-collected vaginal swab specimens* and male and female urine specimens. The assay may be used to test specimens from symptomatic and asymptomatic individuals to aid in the diagnosis of gonococcal and/or chlamydial urogenital disease.

*Patient-collected vaginal swab specimens are an option for screening women when a pelvic exam is not otherwise indicated. The vaginal swab specimen collection kit is not for home use.

Ancillary Kit package insert:

The APTIMA Vaginal Swab Specimen Collection Kit is for use with the APTIMA Assays for the detection of *Chlamydia trachomatis* and *Neisseria gonorrhoeae*. The APTIMA Vaginal Swab Specimen Collection Kit is intended to be used for clinician and patient collection of vaginal swab specimens according to the instructions provided. Patient-collected vaginal swab specimens are an option for screening women when a pelvic exam is not otherwise indicated. The APTIMA Vaginal Swab Specimen Collection Kit is not for home use.

Summary of Technological Characteristics of the APTIMA Combo 2 Assay

The APTIMA Combo 2 Assay incorporates the technologies of target capture, *in vitro* nucleic acid amplification, and hybridization of target amplicons with acridinium ester-labeled DNA probes to specifically detect and differentiate both *C. trachomatis* and *N. gonorrhoeae* nucleic acids in clinical specimens. GEN-PROBE's proprietary technologies are combined in this product to allow qualitative detection of *C. trachomatis* rRNA and *N. gonorrhoeae* rRNA.

Analytical Sensitivity

Chlamydia trachomatis analytical sensitivity (limits of detection) was determined by directly comparing dilutions of *C. trachomatis* organisms in cell culture and in the assay. The analytical sensitivity claim for the assay is one Inclusion-Forming Unit (IFU) per assay (7.25 IFU/swab, 5 IFU/mL urine) for all 15 *C. trachomatis* serovars. However, dilutions of less than one IFU/assay of all serovars tested positive in the APTIMA Combo 2 Assay.

Neisseria gonorrhoeae analytical sensitivity was determined by directly comparing dilutions of 57 different clinical isolates in culture and in the APTIMA Combo 2 Assay. The analytical sensitivity claim for the assay is 50 cells/assay (362 cells/swab, 250 cells/mL urine). However, all strains tested were positive at less than 50 cells/assay.

Analytical Specificity

A total of 154 culture isolates were evaluated using the APTIMA Combo 2 Assay. These isolates included 86 organisms that may be isolated from the urogenital tract and 68 additional organisms that represent a phylogenetic cross-section of organisms. The tested organisms included bacteria, fungi, yeast, parasites, and viruses. All organisms except *C. psittaci, C. pneumoniae*, and the viruses were tested at $1.0x10^6$ cells/assay in both swab and urine transport medium. *C. psittaci* and *C. pneumoniae* were tested at $1.0x10^5$ IFU/assay. The viruses were tested as follows: (a) herpes simplex viruses I and II: $6.0x10^4$ $TCID_{50}$/assay, (b) human papilloma virus 16: $2.9x10^6$ DNA copies/assay and (c) cytomegalovirus: $1x10^6$ infected cell culture cells/assay. Only *C. trachomatis* and *N. gonorrhoeae* samples produced positive results in the APTIMA Combo 2 Assay. The list of organisms tested is shown in the following table.

Analytical Specificity

ORGANISM	ORGANISM	ORGANISM
Achromobacter xerosis	*Escherichia coli*	*Neisseria mucosa* (3)
Acinetobacter calcoaceticus	*Flavobacterium meningosepticum*	*Neisseria sicca* (3)
Acinetobacter lwoffi	*Fusobacterium nucleatum*	*Neisseria subflava* (14)
Actinomyces israelii	*Gardnerella vaginalis*	*Neisseria perflava*
Actinomyces pyogenes	*Gemella haemolysans*	*Neisseria polysaccharea*
Aerococcus viridans	*Haemophilus ducreyi*	*Paracoccus denitrificans*
Aeromonas hydrophila	*Haemophilus influenzae*	*Peptostreptococcus anaerobius*
Agrobacterium radiobacter	Herpes simplex virus I	*Peptostreptococcus productus*
Alcaligenes faecalis	Herpes simplex virus II	*Plesiomonas shigelloides*
Bacillus subtilis	Human papilloma virus 16	*Propionibacterium acnes*
Bacteriodes fragilis	*Kingella dentrificans*	*Proteus mirabilis*
Bacteriodes ureolyticus	*Kingella kingae*	*Proteus vulgaris*
Bifidobacterium adolescentis	*Klebsiella oxytoca*	*Providencia stuartii*
Bifidobacterium brevi	*Klebsiella pneumoniae*	*Pseudomonas aeruginosa*
Branhamella catarrhalis	*Lactobacillus acidophilus*	*Pseudomonas fluorescens*
Brevibacterium linens	*Lactobacillus brevis*	*Pseudomonas putida*
Campylobacter jejuni	*Lactobacillus jensonii*	*Rahnella aquatilis*
Candida albicans	*Lactobacillus lactis*	*Rhodospirillum rubrum*
Candida glabrata	*Legionella pneumophila* (2)	*Saccharomyces cerevisiae*
Candida parapsilosis	*Leuconostoc paramensenteroides*	*Salmonella minnesota*
Candida tropicalis	*Listeria monocytogenes*	*Salmonella typhimurium*
Chlamydia pneumoniae	*Micrococcus luteus*	*Serratia marcescens*
Chlamydia psittaci (2)	*Moraxella lacunata*	*Staphylococcus saprophyticus*
Chromobacterium violaceum	*Moraxella osloensis*	*Staphylococcus aureus*
Citrobacter freundii	*Morganella morganii*	*Staphylococcus epidermidis*
Clostridium perfringens	*Mycobacterium smegmatis*	*Streptococcus agalactiae*
Corynebacterium genitalium	*Mycoplasma genitalium*	*Streptococcus bovis*
Corynebacterium xerosis	*Mycoplasma hominis*	*Streptococcus mitis*
Cryptococcus neoformans	*N. meningitidis* Serogroup A	*Streptococcus mutans*
Cytomegalovirus	*N. meningitidis* Serogroup B	*Streptococcus pneumoniae*
Deinococcus radiodurans	*N. meningitidis* Serogroup C (4)	*Streptococcus pyogenes*
Derxia gummosa	*N. meningitidis* Serogroup D	*Streptococcus salivarius*
Eikenella corrodens	*N. meningitidis* Serogroup Y	*Streptococcus sanguis*
Enterobacter aerogenes	*N. meningitidis* Serogroup W135	*Streptococcus griseinus*
Enterobacter cloacae	*Neisseria cinerea* (4)	*Trichomonas vaginalis*
Entercoccus avium	*Neisseria dentrificans*	*Ureaplasma urealyticum*
Entercoccus faecalis	*Neisseria elongata* (3)	*Vibrio parahaemolyticus*
Entercoccus faecium	*Neisseria flava*	*Yersinia enterocolitica*
Erwinia herbicola	*Neisseria flavescens* (2)	
Erysipelothrix rhusiopathiae	*Neisseria lactamica* (9)	

(n) = number of strains tested

All organisms tested produced a negative result in the APTIMA Combo 2 Assay based on kinetic profile type and RLU.

Interference Studies

The following table lists the commonly encountered substances found in vaginal swab specimens that were tested in the assay. All were tested for potential assay interference in the absence and presence of *C. trachomatis* and *N. gonorrhoeae* at the estimated rRNA equivalent of one *C. trachomatis* IFU/assay (5 fg/assay) and 50 *N. gonorrhoeae* cells/assay (250 fg/assay). The rRNA equivalents were calculated based on the genome size and estimated DNA:RNA ratio/cell of each organism.

Interfering Substances Testing

Swab	Urine
10% Blood	30% Blood
Contraceptive jelly	Urine analytes:
Spermicide	Protein
Moisturizer	Glucose
Hemorrhoidal anesthetic	Ketones
Body oil	Bilirubin
Powder	Nitrate
Anti-fungal cream	Urobilinogen
Vaginal lubricants	pH 4 (acidic)
Feminine spray	pH 9 (alkaline)
Leukocytes (1×10^6 cells/mL)	Leukocytes (1×10^6 cells/mL)
	Cellular debris
	Vitamins
	Minerals
	Acetaminophen
	Aspirin
	Ibuprofen

No interference was observed with any of the tested substances.

Recovery

Lactobacillus acidophilus, *Gardnerella vaginalis*, *Bacteroides ureolyticus* and *Staphylococcus epidermidis* (1 x 10^8 cells/assay) were added to pooled negative vaginal swab samples containing the rRNA equivalent of approximately one *C. trachomatis* IFU (5 fg) and 50 *N. gonorrhoeae* cells (250 fg). These additions did not interfere with the amplification and detection of *C. trachomatis* or *N. gonorrhoeae* rRNA using the APTIMA Combo 2 Assay.

Vaginal Swab Specimen Clinical Study Results

In the vaginal swab specimen multi-center clinical study, 1,464 symptomatic and asymptomatic female subjects attending STD, OB/GYN, teen, and family planning clinics were enrolled into the clinical study. Subjects were classified as symptomatic if symptoms such as discharge, dysuria, and pelvic pain were reported by the subject. Subjects were classified as asymptomatic if the subject did not report symptoms. Of the 646 asymptomatic subjects enrolled in the study, two were less than 16 years of age, 158 were between the ages of 16 and 20, 231 were between the ages of 21 and 25, and 255 were greater than 25 years of age. Of the 818 symptomatic subjects enrolled in the study, 160 were between the ages of 16 and 20, 324 were between the ages of 21 and 25, and 334 were greater than 25 years of age.

Five specimens were collected from each eligible subject; one urine specimen, one patient-collected vaginal swab, one clinician-collected vaginal swab, and two randomized endocervical swabs. APTIMA Combo 2 Assay results were generated from the two vaginal swabs, one of the endocervical swabs, and an aliquot of the urine specimen. The second endocervical swab and a second aliquot of the urine specimen were tested using another commercially-available nucleic acid amplification test (NAAT) for *C. trachomatis* and another commercially-available NAAT for *N. gonorrhoeae*. Endocervical swab and urine specimens tested in the APTIMA Combo 2 Assay and the other commercially available NAATs were used as reference NAATs to determine infected status for each subject in the vaginal swab specimen clinical study.

Specimen testing was conducted either at the site of subject enrollment or at an external testing site.

All performance calculations were based on the total number of APTIMA Combo 2 Assay patient- and clinician-collected vaginal swab results compared to a patient infected status algorithm. A total of 2,868 *C. trachomatis* and 2,867 *N. gonorrhoeae* vaginal swab test results were used in the data analysis. In the algorithm, the designation of a subject as being infected or not infected with *C. trachomatis* or *N. gonorrhoeae* was based on endocervical swab and urine specimen results from the commercially-available APTIMA Combo 2 Assay and the other commercially-available NAAT. Subjects were considered infected with *C. trachomatis* or *N. gonorrhoeae* if two of the four endocervical swab and urine specimens tested positive in the APTIMA Combo 2 Assay and the other reference NAAT (one specimen testing positive in each NAAT). Subjects were considered non-infected if less than two reference NAAT results were positive. Tables 1 and 2 summarize the number of results from symptomatic and asymptomatic subjects designated as infected or non-infected with *C. trachomatis* or *N. gonorrhoeae*, respectively, according to the patient infected status algorithm. For this clinical study, two commercially available NAATs were used to determine GC-infected status. Culture was not used as a reference test since the APTIMA Combo 2 Assay has already been evaluated against culture for other specimen types (refer to K003395).

Sensitivity and specificity for *C. trachomatis* by gender, specimen type and symptom status are presented in Table 3. Table 4 shows the APTIMA Combo 2 Assay sensitivity, specificity, and predictive values for *C. trachomatis* compared to patient infected status for each clinical site and overall. Sensitivity and specificity for detection of *N. gonorrhoeae* by gender, specimen type and symptom status are presented in Table 5. Table 6 shows the *N. gonorrhoeae* sensitivity, specificity, and predictive values for the APTIMA Combo 2 Assay compared to patient infected status for each clinical site and overall. Samples that were APTIMA Combo 2 Assay positive and infected patient status negative (i.e., apparent false positives) were tested in alternate TMA assays for *C. trachomatis* and *N. gonorrhoeae* that targeted sequences unique

from those targeted in APTIMA Combo 2. The results of the alternate TMA assays were not used to change the original patient categorizations (Tables 3 and 5).

Of the 1,464 subjects enrolled, there were 13 subjects with unknown CT patient infected status and 14 subjects with unknown GC patient infected status. Subjects were designated with an unknown patient infected status if results were missing that prevented conclusive determination of infected status. These subjects' results were not included in any performance calculations. Of the 5,782 APTIMA Combo 2 Assay vaginal swab results from the multi-center clinical study, there was a small percentage (28, 0.5%) of vaginal swab specimens that initially tested invalid or equivocal for CT or GC. Upon repeat testing only three *C. trachomatis* results and two *N. gonorrhoeae* results were equivocal and were excluded from the analysis. No specimens tested invalid on repeat testing.

Table 1: *C. trachomatis* Patient- and Clinician-Collected Vaginal Swab Specimen Analysis for Female Patient Infected Status

Patient Infected Status	NAAT 1		NAAT 2 (APTIMA Combo 2 Assay)		APTIMA Combo 2 Assay		Symptom Status		Total
	Endocervical Swab	Urine	Endocervical Swab	Urine	Patient-Collected Vaginal Swab	Clinician-Collected Vaginal Swab	Symptomatic	Asymptomatic	
Infected	+	+	+	+	+	+	79	43	122
Infected	+	+	+	+	+	-	0	1	1
Infected	+	+	+	+	-	+	1	0	1
Infected	+	+	+	+	N/A	-	1	0	1
Infected	+	-	+	+	+	+	8	5	13
Infected	+	-	+	+	-	-	1	0	1
Infected	+	-	+	+	N/A	+	1	0	1
Infected	+	=	+	+	+	+	1	0	1
Infected	-	+	+	+	+	+	8	3	11
Infected	-	+	+	+	-	-	1	0	1
Infected	-	-	+	+	+	+	1	2	3
Infected	-	N/A	+	+	+	+	1	0	1
Infected	+	+	+	-	+	+	5	3	8
Infected	+	-	+	-	+	+	5	0	5
Infected	+	-	+	-	-	+	2	0	2
Infected	+	+	-	+	+	+	0	1	1
Infected	-	+	-	+	+	+	1	4	5
Infected	-	+	-	+	+	-	1	0	1
Infected	-	+	-	+	-	-	0	1	1
Non-infected	-	-	+	-	+	+	0	4	4
Non-infected	-	-	+	-	+	-	2	1	3
Non-infected	-	-	+	-	-	+	2	1	3
Non-infected	-	-	+	-	-	-	6	4	10
Non-infected	-	-	+	-	N/A	+	1	0	1
Non-infected	-	-	+	-	N/A	-	1	0	1
Non-infected	-	-	-	+	+	+	4	2	6
Non-infected	-	-	-	+	+	-	1	0	1
Non-infected	-	-	-	+	-	-	0	2	2
Non-infected	+	-	-	-	-	-	1	1	2
Non-infected	-	+	-	-	-	-	1	2	3
Non-infected	-	-	-	-	+	+	3	2	5

Patient Infected Status	NAAT 1		NAAT 2 (APTIMA Combo 2 Assay)		APTIMA Combo 2 Assay		Symptom Status		Total
	Endocervical Swab	Urine	Endocervical Swab	Urine	Patient-Collected Vaginal Swab	Clinician-Collected Vaginal Swab	Symptomatic	Asymptomatic	
Non-infected	-	-	-	-	+	-	2	7	9
Non-infected	-	-	-	-	-	+	12	3	15
Non-infected	-	-	-	-	-	-	623	516	1139
Non-infected	-	-	-	-	-	N/A	0	2	2
Non-infected	-	-	-	-	-	=	1	0	1
Non-infected	-	-	-	-	N/A	+	0	1	1
Non-infected	-	-	-	-	N/A	-	11	8	19
Non-infected	-	-	-	-	N/A	N/A	1	0	1
Non-infected	-	-	-	-	N/A	=	0	1	1
Non-infected	-	-	-	-	=	+	0	1	1
Non-infected	-	N/A	-	-	-	-	2	2	4
Non-infected	-	N/A	-	-	N/A	-	0	1	1
Non-infected	-	=	-	-	-	-	12	9	21
Non-infected	-	=	-	-	-	N/A	0	1	1
Non-infected	=	-	-	-	-	-	1	1	2
Non-infected	-	-	-	N/A	-	-	0	1	1
Non-infected	-	-	N/A	-	-	-	5	4	9
Non-infected	-	-	=	-	-	+	1	0	1
Non-infected	-	-	=	-	-	-	1	0	1
Total							811	640	1451

N/A = Specimen not obtained or available for testing
= represents equivocal on repeat testing

Table 2: *N. gonorrhoeae* Patient- and Clinician-Collected Vaginal Swab Specimen Analysis for Female Patient Infected Status

Patient Infected Status	NAAT 1		NAAT 2 (APTIMA Combo 2 Assay)		APTIMA Combo 2 Assay		Symptom Status		Total
	Endocervical Swab	Urine	Endocervical Swab	Urine	Patient-Collected Vaginal Swab	Clinician-Collected Vaginal Swab	Symptomatic	Asymptomatic	
Infected	+	+	+	+	+	+	44	15	59
Infected	+	+	+	+	+	-	1	0	1
Infected	+	+	+	+	N/A	+	0	1	1
Infected	+	-	+	+	+	+	2	2	4
Infected	+	N/A	+	+	+	+	1	0	1
Infected	-	+	+	+	+	+	1	1	2
Infected	-	-	+	+	+	+	1	1	2
Infected	+	+	+	-	+	+	1	0	1
Infected	+	-	+	-	+	+	1	1	2
Infected	+	-	+	-	+	-	1	0	1
Infected	+	+	-	+	+	+	1	0	1
Infected	-	+	-	+	+	+	0	1	1
Infected	-	+	-	+	+	-	0	1	1
Infected	+	+	-	-	-	+	1	0	1
Non-infected	-	-	+	-	-	-	5	1	6
Non-infected	-	-	-	+	-	-	1	0	1
Non-infected	+	-	-	-	+	+	1	0	1
Non-infected	+	-	-	-	-	-	5	2	7
Non-infected	-	+	-	-	+	+	0	1	1
Non-infected	-	+	-	-	-	-	2	1	3
Non-infected	-	-	-	-	+	+	2	0	2
Non-infected	-	-	-	-	+	-	1	1	2
Non-infected	-	-	-	-	-	+	2	2	4
Non-infected	-	-	-	-	-	-	698	577	1275
Non-infected	-	-	-	-	-	N/A	0	2	2
Non-infected	-	-	-	-	-	=	2	0	2
Non-infected	-	-	-	-	N/A	-	15	9	24
Non-infected	-	-	-	-	N/A	N/A	1	0	1
Non-infected	-	N/A	-	-	-	-	2	2	4
Non-infected	-	N/A	-	-	N/A	-	0	1	1
Non-infected	-	=	-	-	-	-	11	10	21

Patient Infected Status	NAAT 1		NAAT 2 (APTIMA Combo 2 Assay)		APTIMA Combo 2 Assay		Symptom Status		Total
	Endocervical Swab	Urine	Endocervical Swab	Urine	Patient-Collected Vaginal Swab	Clinician-Collected Vaginal Swab	Symptomatic	Asymptomatic	
Non-infected	-	=	-	-	-	N/A	0	1	1
Non-infected	=	-	-	-	-	-	1	1	2
Non-infected	-	-	-	N/A	-	-	0	1	1
Non-infected	-	-	N/A	-	-	-	5	4	9
Non-infected	-	-	=	-	-	-	1	1	2
Total							810	640	1450

N/A = Specimen not obtained or available for testing
= represents equivocal on repeat testing

Table 3: *C. trachomatis* Sensitivity and Specificity: APTIMA Combo 2 Assay Vaginal Swab Specimens vs. Patient Infected Status

Specimen	Symptom Status	N	TP	FP[1]	TN	FN	Sensitivity (95% C.I.)		Specificity (95% C.I.)	
Patient-Collected Vaginal Swab	Asymptomatic	628	62	16[a]	549	1	98.4	(91.5 - 100)	97.2	(95.4 - 98.4)
	All	1423	172	28[b]	1217	6	96.6	(92.8 - 98.8)	97.8	(96.8 - 98.5)
Clinician-Collected Vaginal Swab	Symptomatic	809	113	23[c]	669	4	96.6	(91.5 - 99.1)	96.7	(95.1 - 97.9)
	Asymptomatic	636	61	14[d]	559	2	96.8	(89.0 - 99.6)	97.6	(95.9 - 98.7)
	All	1445	174	37[e]	1228	6	96.7	(92.9 - 98.8)	97.1	(96.0 - 97.9)

[1]CT TMA Alternate Amplification results: # positive results/# specimens tested
a: 13/16 b: 24/28 c: 15/23 d: 13/14 e: 28/37

Table 4: *C. trachomatis* Performance by Clinical Site: APTIMA Combo 2 Assay Vaginal Swab Specimens vs. Patient Infected Status

Specimen	Site	N	TP	FP	TN	FN	Prev (%)	Sensitivity	(95% C.I.)	Specificity	(95% C.I.)	PPV (%)	NPV (%)
Patient-Collected	1	218	34	6	177	1	16.1	97.1	(85.1 - 99.9)	96.7	(93.0 - 98.8)	85.0	99.4
Vaginal Swab	2	195	50	6	137	2	26.7	96.2	(86.8 - 99.5)	95.8	(91.1 - 98.4)	89.3	98.6
	3	111	10	1	100	0	9.0	100	(69.2 - 100)	99.0	(94.6 - 100)	90.9	100
	4	261	20	4	236	1	8.0	95.2	(76.2 - 99.9)	98.3	(95.8 - 99.5)	83.3	99.6
	5	199	13	3	183	0	6.5	100	(75.3 - 100)	98.4	(95.4 - 99.7)	81.3	100
	6	290	32	5	251	2	11.7	94.1	(80.3 - 99.3)	98.0	(95.5 - 99.4)	86.5	99.2
	7	102	10	2	90	0	9.8	100	(69.2 - 100)	97.8	(92.4 - 99.7)	83.3	100
	8	47	3	1	43	0	6.4	100	(29.2 - 100)	97.7	(88.0 - 99.9)	75.0	100
	ALL	1423	172	28	1217	6	12.5	96.6	(92.8 - 98.8)	97.8	(96.8 - 98.5)	86.0	99.5
Clinician-Collected	1	227	35	8	182	2	16.3	94.6	(81.8 - 99.3)	95.8	(91.9 - 98.2)	81.4	98.9
Vaginal Swab	2	196	50	5	139	2	26.5	96.2	(86.8 - 99.5)	96.5	(92.1 - 98.9)	90.9	98.6
	3	113	10	2	101	0	8.8	100	(69.2 - 100)	98.1	(93.2 - 99.8)	83.3	100
	4	262	20	10	231	1	8.0	95.2	(76.2 - 99.9)	95.9	(92.5 - 98.0)	66.7	99.6
	5	199	13	2	184	0	6.5	100	(75.3 - 100)	98.9	(96.2 - 99.9)	86.7	100
	6	296	34	8	254	0	11.5	100	(89.7 - 100)	96.9	(94.1 - 98.7)	81.0	100
	7	102	9	1	91	1	9.8	90.0	(55.5 - 99.7)	98.9	(94.1 - 100)	90.0	98.9
	8	50	3	1	46	0	6.0	100	(29.2 - 100)	97.9	(88.7 - 99.9)	75.0	100
	ALL	1445	174	37	1228	6	12.5	96.7	(92.9 - 98.8)	97.1	(96.0 - 97.9)	82.5	99.5

Table 5: *N. gonorrhoeae* Sensitivity and Specificity: APTIMA Combo 2 Assay Vaginal Swab Specimens vs. Patient Infected Status

Specimen	Symptom Status	N	TP	FP[1]	TN	FN	Sensitivity	(95% C.I.)	Specificity	(95% C.I.)
Patient-Collected Vaginal Swab	Asymptomatic	629	22	2[a]	605	0	100	(84.6 - 100)	99.7	(98.8 - 100)
	All	1423	76	6[b]	1340	1	98.7	(93.0 - 100)	99.6	(99.0 - 99.8)
Clinician-Collected Vaginal Swab	Symptomatic	807	53	5[c]	747	2	96.4	(87.5 - 99.6)	99.3	(98.5 - 99.8)
	Asymptomatic	637	22	3[d]	611	1	95.7	(78.1 - 99.9)	99.5	(98.6 - 99.9)
	All	1444	75	8[e]	1358	3	96.2	(89.2 - 99.2)	99.4	(98.8 - 99.7)

[1]GC TMA Alternate Amplification results: # positive results/# specimens tested
a: 2/2 b: 6/6 c: 5/5 d: 2/3 e: 7/8

Table 6: *N. gonorrhoeae* Performance by Clinical Site: APTIMA Combo 2 Assay Vaginal Swab Specimens vs. Patient Infected Status

Specimen	Site	N	TP	FP	TN	FN	Prev (%)	Sensitivity	(95% C.I.)	Specificity	(95% C.I.)	PPV (%)	NPV (%)
Patient-Collected	1	217	13	0	203	1	6.5	92.9	(66.1 - 99.8)	100	(98.2 - 100)	100	99.5
Vaginal Swab	2	196	31	1	164	0	15.8	100	(88.8 - 100)	99.4	(96.7 - 100)	96.9	100
	3	111	4	0	107	0	3.6	100	(39.8 - 100)	100	(96.6 - 100)	100	100
	4	261	5	1	255	0	1.9	100	(47.8 - 100)	99.6	(97.8 - 100)	83.3	100
	5	199	2	0	197	0	1.0	100	(15.8 - 100)	100	(98.1 - 100)	100	100
	6	290	20	4	266	0	6.9	100	(83.2 - 100)	98.5	(96.3 - 99.6)	83.3	100
	7	102	0	0	102	0	0.0	N/A	N/A	100	(96.4 - 100)	N/A	100
	8	47	1	0	46	0	2.1	100	(2.5 - 100)	100	(92.3 - 100)	100	100
	ALL	1423	76	6	1340	1	5.4	98.7	(93.0 - 100)	99.6	(99.0 - 99.8)	92.7	99.9
Clinician-Collected	1	227	15	0	212	0	6.6	100	(78.2 - 100)	100	(98.3 - 100)	100	100
Vaginal Swab	2	196	31	2	163	0	15.8	100	(88.8 - 100)	98.8	(95.7 - 99.9)	93.9	100
	3	113	3	0	109	1	3.5	75.0	(19.4 - 99.4)	100	(96.7 - 100)	100	99.1
	4	262	5	2	255	0	1.9	100	(47.8 - 100)	99.2	(97.2 - 99.9)	71.4	100
	5	198	2	0	196	0	1.0	100	(15.8 - 100)	100	(98.1 - 100)	100	100
	6	296	18	4	272	2	6.8	90.0	(68.3 - 98.8)	98.6	(96.3 - 99.6)	81.8	99.3
	7	102	0	0	102	0	0.0	N/A	N/A	100	(96.4 - 100)	N/A	100
	8	50	1	0	49	0	2.0	100	(2.5 - 100)	100	(92.7 - 100)	100	100
	ALL	1444	75	8	1358	3	5.4	96.2	(89.2 - 99.2)	99.4	(98.8 - 99.7)	90.4	99.8

Prevalence

The prevalence of *C. trachomatis* and/or *N. gonorrhoeae* disease in patient populations depends on risk factors such as age, gender, the presence of symptoms, the type of clinic, and the test method. A summary of the prevalence of three *C. trachomatis* and *N. gonorrhoeae* disease outcomes as determined by the APTIMA Combo 2 Assay is shown in Table 7 for the vaginal swab specimen multi-center clinical study by clinical site and overall.

Table 7: Prevalence of *C. trachomatis* and/or *N. gonorrhoeae* Disease as Determined by the APTIMA Combo 2 Assay Results by Clinical Site

Site	Patient-Collected Vaginal Swab, % Prevalence (# positive/# tested)						Clinician-Collected Vaginal Swab, % Prevalence (# positive/# tested)					
	CT+/GC+		CT+/GC-		CT-/GC+		CT+/GC+		CT+/GC-		CT-/GC+	
1	1.8	(4/220)	16.4	(36/220)	4.1	(9/220)	3	(7/230)	15.7	(36/230)	3.5	(8/230)
2	9.6	(19/198)	18.7	(37/198)	6.6	(13/198)	9.5	(19/199)	18.1	(36/199)	7	(14/199)
3	0.9	(1/111)	9	(10/111)	2.7	(3/111)	0.9	(1/113)	9.7	(11/113)	1.8	(2/113)
4	0.4	(1/266)	9	(24/266)	1.9	(5/266)	0.4	(1/267)	11.2	(30/267)	2.2	(6/267)
5	0.5	(1/199)	7.5	(15/199)	0.5	(1/199)	0.5	(1/199)	7	(14/199)	0.5	(1/199)
6	2.8	(8/290)	10	(29/290)	5.5	(16/290)	2	(6/296)	12.2	(36/296)	5.4	(16/296)
7	0	(0/102)	11.8	(12/102)	0	(0/102)	0	(0/102)	9.8	(10/102)	0	(0/102)
8	0	(0/48)	8.3	(4/48)	2.1	(1/48)	0	(0/51)	7.8	(4/51)	2	(1/51)
All	2.4	(34/1434)	11.6	(167/1434)	3.3	(48/1434)	2.4	(35/1457)	12.1	(177/1457)	3.3	(48/1457)

Positive and Negative Predictive Values for Hypothetical Prevalence Rates

The estimated positive and negative predictive values (PPV and NPV) for different hypothetical prevalence rates using the APTIMA Combo 2 Assay are shown in Tables 8 and 9 for *C. trachomatis* and *N. gonorrhoeae*, respectively. These calculations are based on a hypothetical prevalence and the overall sensitivity and specificity calculated from the patient infected status for two multi-center clinical studies; the endocervical swab, male urethral swab, and urine specimen clinical study and the vaginal swab specimen clinical study. The overall sensitivity and specificity for *C. trachomatis* was 96.1% and 97.9%, respectively (Table 8). The overall sensitivity and specificity for *N. gonorrhoeae* was 98.0% and 99.1%, respectively (Table 9). The actual PPV and NPV calculated using the clinical study data are shown in Tables 4 and 6 for *C. trachomatis* and *N. gonorrhoeae*, respectively

Table 8: Positive and Negative Predictive Values for Hypothetical Prevalence Rates- *C. trachomatis*

Prevalence Rate (%)	Sensitivity (%)	Specificity (%)	Positive Predictive Value (%)	Negative Predictive Value (%)
2	95.9	98.2	52.1	99.9
5	95.9	98.2	73.7	99.8
10	95.9	98.2	85.5	99.5
15	95.9	98.2	90.4	99.3
20	95.9	98.2	93.0	99.0
25	95.9	98.2	94.7	98.6
30	95.9	98.2	95.8	98.2

Table 9: Positive and Negative Predictive Values for Hypothetical Prevalence Rates- *N. gonorrhoeae*

Prevalence Rate (%)	Sensitivity (%)	Specificity (%)	Positive Predictive Value (%)	Negative Predictive Value (%)
2	97.8	98.9	64.5	100
5	97.8	98.9	82.4	99.9
10	97.8	98.9	90.8	99.8
15	97.8	98.9	94.0	99.6
20	97.8	98.9	95.7	99.4
25	97.8	98.9	96.7	99.3
30	97.8	98.9	97.4	99.1

Assay Control Performance

Control RLU data were generated as part of the vaginal swab specimen clinical study. A summary of the APTIMA Positive Control, CT/Negative Control, GC and APTIMA Positive Control, GC/Negative Control, CT performance during the clinical study is presented in Table 10.

Table 10: Distribution of Total RLU of the APTIMA Assay Controls from the Vaginal Swab Specimen Clinical Study

Control	Statistics	Total RLU (x1000)
Positive, CT/Negative, GC	Maximum	1996
	75th Percentile	1279
	Median	1135
	25th Percentile	933
	Minimum	174
Positive, GC/Negative, CT	Maximum	1420
	75th Percentile	1255
	Median	1169
	25th Percentile	1084
	Minimum	249

Conclusions from the Clinical Data

The non-clinical and clinical study results support the use of clinician-collected and patient-collected vaginal swab specimens in the GEN-PROBE APTIMA Combo 2 Assay for the detection of *C. trachomatis* and *N. gonorrhoeae*. The GEN-PROBE APTIMA Vaginal Swab Specimen Collection Kit provides the necessary materials to allow for the testing of clinician-collected or patient-collected vaginal specimens in the APTIMA Combo 2 Assay. Use of this ancillary kit broadens the application of the APTIMA Combo 2 Assay as a diagnostic tool to provide information that measurably contributes to a diagnosis of *C. trachomatis* and *N. gonorrhoeae* infection.

The results of the clinical study demonstrate reasonable evidence that when the APTIMA Combo 2 Assay and the APTIMA Vaginal Swab Specimen Collection Kit are labeled as proposed, the GEN-PROBE APTIMA Combo 2 Assay is safe and effective for its stated intended use.

Application of the APTIMA Vaginal Swab Specimen Collection kit in the APTIMA Combo 2 Assay provides performance that is substantially equivalent to that of the previously cleared claims (K003395) for the detection of *C. trachomatis* and *N. gonorrhoeae* which is indicative of it's safety and effectiveness.

Contraindications and Cautions

There are no contraindications or cautions.

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
2098 Gaither Road
Rockville MD 20850

DEC 31 2003

Alan Maderazo, Ph.D. RAC
Regulatory Affairs Specialist
Gen-Probe Incorporated
10210 Genetic Center Drive
San Diego, CA 92121-1589

Re: k032554
Trade/Device Name: GEN-PROBE® APTIMA® Combo 2 Assay
Regulation Number: 21 CFR 866.3390
Regulation Name: Neisseria spp. Direct Serological Test Reagents
Regulatory Class: Class II
Product Code: LSL, MKZ
Dated: December 24, 2003
Received: December 29, 2003

Dear Dr. Maderazo:

We have reviewed your Section 510(k) premarket notification of intent to market the device referenced above and have determined the device is substantially equivalent (for the indications for use stated in the enclosure) to legally marketed predicate devices marketed in interstate commerce prior to May 28, 1976, the enactment date of the Medical Device Amendments, or to devices that have been reclassified in accordance with the provisions of the Federal Food, Drug, and Cosmetic Act (Act) that do not require approval of a premarket approval application (PMA). You may, therefore, market the device, subject to the general controls provisions of the Act. The general controls provisions of the Act include requirements for annual registration, listing of devices, good manufacturing practice, labeling, and prohibitions against misbranding and adulteration.

If your device is classified (see above) into either class II (Special Controls) or class III (PMA), it may be subject to such additional controls. Existing major regulations affecting your device can be found in Title 21, Code of Federal Regulations (CFR), Parts 800 to 895. In addition, FDA may publish further announcements concerning your device in the Federal Register.

Please be advised that FDA's issuance of a substantial equivalence determination does not mean that FDA has made a determination that your device complies with other requirements of the Act or any Federal statutes and regulations administered by other Federal agencies. You must comply with all the Act's requirements, including, but not limited to: registration and listing (21 CFR Part 807); labeling (21 CFR Parts 801 and 809); and good manufacturing practice requirements as set forth in the quality systems (QS) regulation (21 CFR Part 820).

This letter will allow you to begin marketing your device as described in your Section 510(k) premarket notification. The FDA finding of substantial equivalence of your device to a legally marketed predicate device results in a classification for your device and thus, permits your device to proceed to the market.

If you desire specific information about the application of labeling requirements to your device, or questions on the promotion and advertising of your device, please contact the Office of In Vitro Diagnostic Device Evaluation and Safety at (301) 594-3084. Also, please note the regulation entitled, "Misbranding by reference to premarket notification" (21CFR Part 807.97). Other general information on your responsibilities under the Act may be obtained from the Division of Small Manufacturers, International and Consumer Assistance at its toll-free number (800) 638-2041 or (301) 443-6597 or at its Internet address http://www.fda.gov/cdrh/dsma/dsmamain.html.

Sincerely yours,

Steven Gutman

Steven I. Gutman, M.D., M.B.A.
Director
Office of *In Vitro* Diagnostic Device
Evaluation and Safety
Center for Devices and
Radiological Health

Enclosure

Indications for Use

510(k) Number (if known): K032554

Device Name: GEN-PROBE® APTIMA® Combo 2 Assay

Indications for Use (AC2 Assay package insert):

The APTIMA Combo 2 Assay is a target amplification nucleic acid probe test that utilizes target capture for the *in vitro* qualitative detection and differentiation of ribosomal ribonucleic acid (rRNA) from *Chlamydia trachomatis* and/or *Neisseria gonorrhoeae* in clinician-collected endocervical, vaginal, and male urethral swab specimens, patient-collected vaginal swab specimens* and male and female urine specimens. The assay may be used to test specimens from symptomatic and asymptomatic individuals to aid in the diagnosis of gonococcal and/or chlamydial urogenital disease.

*Patient-collected vaginal swab specimens are an option for screening women when a pelvic exam is not otherwise indicated. The vaginal swab specimen collection kit is not for home use.

Indications for Use (Ancillary Kit package insert):

The APTIMA Vaginal Swab Specimen Collection Kit is for use with the APTIMA Assays for the detection of *Chlamydia trachomatis* and *Neisseria gonorrhoeae*. The APTIMA Vaginal Swab Specimen Collection Kit is intended to be used for clinician and patient collection of vaginal swab specimens according to the instructions provided. Patient-collected vaginal swab specimens are an option for screening women when a pelvic exam is not otherwise indicated. The APTIMA Vaginal Swab Specimen Collection Kit is not for home use.

Prescription Use ✓ AND/OR Over-The-Counter Use _____
(Part 21 CFR 801 Subpart D) (21 CFR 807 Subpart C)

(PLEASE DO NOT WRITE BELOW THIS LINE-CONTINUE ON ANOTHER PAGE IF NEEDED)

Concurrence of CDRH, Office of In Vitro Diagnostic Devices (OIVD)

12/31/03

Division Sign-Off

Office of In Vitro Diagnostic Device
Evaluation and Safety

510(k) K032554